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| APPLICATION NO. | FILING DATE | FIRST NAMED INVENTOR | ATTORNEY DOCKET NO. | CONFIRMATION NO. |
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| 09/772,598 | 01/30/2001 | Timothy E. Benson | 6315.N | 2967 |

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MUETING, RAASCH & GEBHARDT, P.A.
P.O. BOX 581415
MINNEAPOLIS, MN 55458

| EXAMINER | |
|---|---|
| MAHATAN, CHANNING | |
| ART UNIT | PAPER NUMBER |
| 1631 | 15 |

DATE MAILED: 10/01/2002

Please find below and/or attached an Office communication concerning this application or proceeding.

| Office Action Summary | Application No. 09/772,598 | Applicant(s) BENSON ET AL. | |
|---|---|---|---|
| | Examiner Channing S. Mahatan | Art Unit 1631 | |

*-- The MAILING DATE of this communication app ars n the cover sheet with th correspondence address --*

**Period for Reply**

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133).
- Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

**Status**

1)☒ Responsive to communication(s) filed on *3 July 2002, Paper No. 9* .

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

**Disposition of Claims**

4)☒ Claim(s) *1-43* is/are pending in the application.

4a) Of the above claim(s) *1-34* is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *35-43* is/are rejected.

7)☒ Claim(s) *35-38* is/are objected to.

8)☒ Claim(s) *1-43* are subject to restriction and/or election requirement.

**Application Papers**

9)☒ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

11)☒ The proposed drawing correction filed on *03 July 2002* is: a)☒ approved b)☐ disapproved by the Examiner.

If approved, corrected drawings are required in reply to this Office action.

12)☐ The oath or declaration is objected to by the Examiner.

**Priority under 35 U.S.C. §§ 119 and 120**

13)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____ .

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

14)☒ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. § 119(e) (to a provisional application).

a) ☐ The translation of the foreign language provisional application has been received.

15)☐ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. §§ 120 and/or 121.

**Attachment(s)**

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO-1449) *5 Sheets* .
4) ☐ Interview Summary (PTO-413) Paper No(s). _____ .
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: .

## DETAILED ACTION

*APPLICANTS' ELECTION*

Applicants' election with traverse of Group XI (claims 35-43; drawn to a crystal of "*Staphylococcus aureus* nicotinamide adenine dinucleotide synthetase" and method for crystallizing an "*Staphylococcus aureus* nicotinamide adenine dinucleotide synthetase") in Paper No. 9, filed 03 July 2002, is acknowledged. The traversal is on the grounds that the inventions as claimed can be readily evaluated in one search without placing undue burden on the Examiner. Applicant's argument is found unpersuasive because the restriction/election requirement in Paper No. 7, mailed 05 June 2002, indicated the specific distinction between the multiple inventions (i.e. product and process of use), thus demonstrating that the inventions are distinct, establishing a separate status in the art, and a different field of search. The requirement is still deemed proper and is therefore made FINAL. Claims 1-34 are withdrawn from examination as not directed to the elected invention.

*CLAIMS UNDER EXAMINATION*

Claims herein under examination are claims 35-43.

### Claims Rejected Under 35 U.S.C. § 112 1st Paragraph

The following is a quotation of the first paragraph of 35 U.S.C. § 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

Factors to be considered in determining whether a disclosure would require undue experimentation have been summarized in Ex parte Forman, 230 USPQ 546 (BPAI 1986) and reiterated by the Court of Appeals in In re Wands, 8 USPQ2d 1400 at 1404 (CAFC 1988). The

factors to be considered in determining whether undue experimentation is required include: (1) the quantity of experimentation necessary, (2) the amount or direction presented, (3) the presence or absence of working examples, (4) the nature of the invention, (5) the state of the prior art, (6) the relative skill of those in the art, (7) the predictability or unpredictability of the art, and (8) the breadth of the claims. The Board also stated that although the level of skill in molecular biology is high, the results of experiments in genetic engineering are unpredictable. While all of these factors are considered, a sufficient amount for a *prima facie* case are discussed below.

*LACK OF ENABLEMENT*

Claims 35-43 are rejected under 35 U.S.C. § 112, first paragraph, as containing subject matter which was not described in the specification in such a way as to enable one skilled in the art to which it pertains, or with which it is most nearly connected, to make and/or use the invention.

In the field of protein crystallography, it is well established that the utilization of a variety of crystallization methods, for the protein in question, greatly improves the chances of identifying suitable conditions for crystallization. However, obtaining suitable single crystal(s) is the least understood step in the X-ray structural analysis of a protein(s). Therefore, since the science of protein crystallization is underdeveloped, the crystallization of a protein is mainly a trial-and-error procedure. Further, it is well known that the homologous proteins from different sources cannot be easily crystallized using the same techniques and/or conditions and may result in different crystal forms. See, for example, Jan Drenth ("Principles of Protein X-ray Crystallography", pages 1-9).

Although it appears that applicants are in possession of the crystal of "*Staphylococcus aureus* nicotinamide adenine dinucleotide synthetase" applicants have failed to indicate suitable conditions for the crystallization of "*Staphylococcus aureus* nicotinamide adenine dinucleotide synthetase". The recitation of conditions that prevents/inhibits a method of crystallization does not provide enablement. Applicants indicate for example: 1) "...several attempts were made to introduce pH buffers into the system, however, yielding poor crystals or precipitated protein"; 2) "Buffer exchanging the protein solution into 100mM Tris, 5mM B-mercaptoethanol, pH 8.0 did not result in crystallization, as the protein precipitated or the drops remained clear" (pages 41-42). Merely stating conditions that do not work fails to provide one of skill in the art proper guidance as to the conditions that do work. Additionally, the disclosure is confusing in that the specification states "...presence of salt restricts crystallization of this protein. Salts stabilize the protein, making it more difficult to bring out of solution", however, claim 36 indicates a salt (i.e. ammonium sulfate) for crystallization. While working examples are not, per se, required, the specification must provide an enabling disclosure for the invention as it is claimed such that one of skill in the art could practice the invention without undue experimentation. Proper disclosure for the conditions for crystallization (i.e. pH, concentration of protein, reagents, etc) is required for enablement. Without setting forth the conditions for the crystallization of "*Staphylococcus aureus* nicotinamide adenine dinucleotide synthetase" one of skill in the art could not make and/or use the invention without undue experimentation. Thus, the above level of disclosure is not present here, nor supplied by the art or knowledge of one skilled in the art, therefore, the breadth of the claims is not enabled.

*LACK OF WRITTEN DESCRIPTION*

Claim 43 is rejected under 35 U.S.C. § 112, first paragraph, as containing subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention.

Present in SEQ ID NO: 1 are numerous methionines to which instant claim 43 requires the replacement of at least one methionine with selenomethionine. Although the replacement of methionine with selenomethionine may or may not result in a protein of different function, one of skill in the art would at least expect such replacement to result in structurally different coordinates. It is noted that selenomethionine differs from methionine in that a selenium atom substitutes the sulfur atom in methionine. Further, the specification fails to indicate which methionine(s) (by position) are replaced (individually and/or in combination). This is a rejection based on a lack of WRITTEN DESCRIPTION.

> Vas-Cath Inc. v. Mahurkar, 19 USPQ2d 1111, makes clear that "applicant must convey with reasonable clarity to those skilled in the art that, as of the filing date sought, he or she was in possession *of the invention.* The invention is, for purposes of the 'written description' inquiry, *whatever is now claimed.*" (See page 1117.) The specification does not "clearly allow persons of ordinary skill in the art to recognize that [he or she] invented what is claimed." (See Vas-Cath at page 1116.)

The skilled artisan cannot envision the detailed structural coordinates of the encompassed proteins, regardless of the complexity or simplicity of the method of expression, incorporation, or isolation. Finally, University of California v. Eli Lilly and Co., 43 USPQ2d 1398, 1404, 1405 held that:

> ...To fulfill the written description requirement, a patent specification must describe an invention and do so in sufficient detail that one skilled in the art can clearly conclude that "the inventor invented the claimed invention." *Lockwood v. American Airlines, Inc.*, 107 F.3d 1565, 1572, 41 USPQ2d 1961, 1966 (1997); *In re Gosteli*, 872 F.2d 1008, 1012, 10 USPQ2d 1614, 1618 (Fed. Cir. 1989) (" [T]he description must clearly allow persons of ordinary skill in the art to recognize that [the inventor] invented what is claimed."). Thus, an applicant complies with the written description requirement "by describing the invention, with all its claimed limitations, not that which makes it obvious," and by using "such descriptive means as words, structures,

> figures, diagrams, formulas, etc., that set forth the claimed invention." *Lockwood*, 107 F.3d at 1572, 41 USPQ2d at 1966.

Therefore, the lack of the structurally coordinates for the replacement of methionine (individually and/or in combination) by selenomethionine for SEQ ID NO: 1, as in instant claim 43, does not meet the written description provision of 35 U.S.C. § 112, first paragraph. Applicants are reminded that Vas-Cath makes clear that the written description provision of 35 U.S.C. § 112 is severable from its enablement provision. (See page 115).

**Claims Rejected Under 35 U.S.C. § 112 2nd Paragraph**

The following is a quotation of the second paragraph of 35 U.S.C. § 112:

> The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

Claims 35-37 are rejected under 35 U.S.C. § 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

*VAGUE AND INDEFINITE*

Claims 35 (line 1), 36 (line 1), and 37 (line 1) recite the phrase "molecular complex" which is vague and indefinite. The above claims are directed to methods for crystallizing an "*Staphylococcus aureus* nicotinamide adenine dinucleotide synthetase" molecule or molecular complex, however, it is unclear as to whether the "molecular complex" is meant to indicate that "*Staphylococcus aureus* nicotinamide adenine dinucleotide synthetase" is in a crystallizable complex. Further, crystallizing a "molecular complex" may or may not include other molecule types. If the "molecular complex" of claims 35-37 is meant to include crystallization of complexes that include molecules other than "*Staphylococcus aureus* nicotinamide adenine dinucleotide synthetase", then it is unclear when these complexes are added in the method steps

of the claims? Additionally, instant claims 35-37 fails to define what is co-crystallized with "*Staphylococcus aureus* nicotinamide adenine dinucleotide synthetase" to a form a "molecular complex". Clarification, via clearer claim wording is required.

**Claims Rejected Under 35 U.S.C. § 102**

The following is a quotation of the appropriate paragraphs of 35 U.S.C. § 102 that form the basis for the rejections under this section made in this Office action:

> A person shall be entitled to a patent unless –
>
> (b) the invention was patented or described in a printed publication in this or a foreign country or in public use or on sale in this country, more than one year prior to the date of application for patent in the United States.

Claims 35-40 are rejected under 35 U.S.C. § 102(b) as being clearly anticipated by Rizzi et al. (Crystallization of $NAD^+$ Synthetase from *Bacillus subtilis*, Proteins: Structure, Function, and Genetics. 1996, Volume 26, pages 236-238). It should be noted that applicant has failed to provide evidence that indicates nicotinamide adenine dinucleotide synthetase from *Staphylococcus aureus* is unique, and is particularly different from all other organisms (i.e. *Bacillus subtilis*).

Rizzi et al. describes the crystallization of nicotinamide adenine dinucleotide synthetase from *Bacillus subtilis* (Abstract). Crystals of nicotinamide adenine dinucleotide synthetase from *Bacillus subtilis* were grown in 22% polyethylene glycol at a pH of 5.2 utilizing a protein concentration of 20 mg/mL (page 236, Column 2, lines 33-37; instant claims 35-38). The crystal belongs to the $P2_1$ space group (instant claim 39) with unit cell dimensions a = 53.0 Å, b = 87.1 Å, c = 60.2 Å and ß =111.1 degrees (instant claim 40) (page 238, Column 1, lines 16-19). Thus, Rizzi et al. clearly anticipates the claimed invention.

*OBJECTION TO CLAIMS*

Claims 35-38 are objected to because of the following informalities:

The utilization of abbreviation(s) in claims is improper. For examination purposes, PEG is regarded to mean "polyethylene glycol"; DMSO is regarded to mean "dimethyl sulfoxide"; *S. aureus* is regarded as "*Staphylococcus aureus*"; and NAD is regarded as "Nicotinamide adenine dinucleotide". Appropriate correction is required.

*OBJECTION TO DISCLOSURE*

The disclosure is objected to because of the following informalities:

The disclosure is objected to because it contains an embedded hyperlink and/or other form of browser-executable code on page 26, line 9. Embedded hyperlinks and/or other form of browser-executable code are impermissible in the text of the application as they represent an improper incorporation by reference. Applicants are required to delete the embedded hyperlink and/or other form of browser-executable code. See M.P.E.P. § 608.01 and § 608.01(p).

The specification on pages 10-11, Tables 3-5, requires line spacing correction. The specification is required to be either double-spaced or at least 1 ½ spaced and not single-spaced.

**Appropriate Correction Is Required.**

**No Claims Are Allowed.**

*EXAMINER INFORMATION*

Papers related to this application may be submitted to Technical Center 1600 by facsimile transmission. Papers should be faxed to Technical Center 1600 via the PTO Fax Center located in Crystal Mall 1. The faxing of such papers must conform with the notices published in the Official Gazette, 1096 OG 30 (November 15, 1988), 1156 OG 61 (November 16, 1993), and

1157 OG 94 (December 28, 1993) (See 37 C.F.R. § 1.6(d)). The CM1 Fax Center number is either (703) 308-4242 or (703) 305-3014.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Channing S. Mahatan whose telephone number is (703) 308-2380. The examiner can normally be reached on M-F (8:30-5:00).

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Michael P. Woodward, Ph.D., can be reached on (703) 308-4028.

Any inquiry of a general nature or relating to the status of this application should be directed to Patent Analyst, William Phillips, whose telephone number is (703) 305-3482 or to the Technical Center receptionist whose telephone number is (703) 308-0196.

Date: September 30, 2002

Examiner Initials: CSM

MICHAEL P. WOODWARD
SUPERVISORY PATENT EXAMINER
TECHNOLOGY CENTER 1600